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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	
09/132,799	08/13/1998	UWE SCHOENROCK	BEIERS.0645	

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EXAMINER
BORIN, MICHAEL L

DATE MAILED: 01/31/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/132,799	Schoenrock et al.
Examiner	**Art Unit**
Michael Borin	1631

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) X Responsive to communication(s) filed on *Jul 31, 2001* .

2a) ___ This action is **FINAL**. 2b) X This action is non-final.

3) ___ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) X Claim(s) *1 and 3-13* is/are pending in the application.

4a) Of the above, claim(s) *5, 7-10, and 13* is/are withdrawn from consideration.

5) ___ Claim(s) _____ is/are allowed.

6) X Claim(s) *1, 3, 4, 6, 11, and 12* is/are rejected.

7) ___ Claim(s) _____ is/are objected to.

8) ___ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ___ The specification is objected to by the Examiner.

10) ___ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ___ The proposed drawing correction filed on _____ is: a) ___ approved b) ___ disapproved.

12) ___ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ___ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ___ All b) ___ Some* c) ___ None of:

1. ___ Certified copies of the priority documents have been received.
2. ___ Certified copies of the priority documents have been received in Application No. _____ .
3. ___ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ___ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) X	Notice of References Cited PTO-892	18) X	Interview Summary PTO 413 Paper No's
16) ___	Notice of Draftsperson's Patent Drawing Review PTO-948	19) ___	Notice of Informal Patent Application PTO-152
17) ___	Information Disclosure Statement s PTO-1449 Paper No s	20) ___	Other

DETAILED ACTION

1. Response filed 07/31/01 is acknowledged. Claims 1,3-13 are pending. Claims 5, 7-10,13 remain withdrawn from consideration. Claims reading on the elected species, 1,3,4,6,11,12 are examined on merits to the extent they read on the monomer oligopeptide VVRP, its amide and/or N-acetyl derivative.

2. In view of applicant's arguments, obviousness rejections are re-stated with the inclusion of secondary references. Applicants arguments are noted but are deemed moot in view of the new grounds of rejection.

Claim Rejections - 35 U.S.C. § 103.

3. Claims 1, 3 rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990) and Stein (US 5,346,887) in view of Goodman & Gilman's "The pharmacological basis of therapeutics" (ninth edition, p. 745) and further in view of Greene et al. (US 5,753,226).

The instant claims, in part defined in claim 1, items (1) and (3), are drawn to water-in-oil preparations comprising peptide VVRP, or peptides comprising said sequence VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention). See p. 835, Table 1, compound No. 6. Further, the

reference teaches peptides comprising said sequence VVRP: AVVRP, PAVVRP, NPAVVRP, ANPAVVRP, YANPAVVRP (i.e., peptides as instantly claimed, wherein ψ= 1÷5, Ω=0). See p. 835, Table 1, compounds No. 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column). Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

Stein (US 5,346,887)

'887 patent teaches topical compositions comprising ACE inhibitors. Said compositions are used for treatment of glaucoma.

It would have been *prima facie* obvious to one skilled in the art at the time the invention was made to be motivated to prepare a topical pharmaceutical composition comprising peptides of Kohmura as an active ingredient, because Kohmura teaches that these peptides inhibit ACE activity and as such they can be used in topical pharmaceutical compositions of Stein. Note that **Goodman & Gilman's "The pharmacological basis of therapeutics"** (ninth edition, p. 743-751; submitted by applicants) teaches that "there is no compelling reason to favor one ACE inhibitor over another, since all ACE inhibitors have ... similar therapeutic indications, adverse effect profiles and contraindications." See p. 745, first full paragraph.

In regard to particular physical form of the preparation, water-in-oil disperison, selection of a particular physical form of preparation is within perview of one skilled in the art. For example, Greene et al. (US 5,753,226) describes peptide formulations for topical treatment of ocular and skin

sites. See col. 14, bottom and claims 1,24. The reference teaches a wide variety of physical forms, most preferable of which being water-in-oil emulsions. Thus, selection of such physical form for topical ocular administration would be obvious to an artisan.

In regard to intended use recited in the preamble of claim 1, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. A mere statement of purpose or intended use in the preamble of a claim need not be considered in finding anticipation Divertech Corp. V. Century Steps, Inc.,7USPQ2d 1315 (Fed. Cir. 1988); In re Stencel, 4 USPQ2d 1071 (Fed. Cir. 1987). The motivation in the prior art to combine references need not be identical to that of the applicant to establish obviousness. In re Kemps, 40 USPQ2d 1309 (Fed. Cir., 1996). Further, the discovery of a new use for a prior art composition based on previously unknown properties of the structure may be patentable if claimed as a method; in the instant case the claims are drawn to a composition.

4. Claims 1, 3 rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al (Agric. Biol. Chem., 54, 835-836, 1990) and Goodman & Gilman's "The pharmacological basis of therapeutics" (ninth edition, p. 745) and further in view of Cho et al (US 5,665,700).

The instant claims, in part defined in claim 1, items (1) and (3), are drawn to water-in-oil preparations comprising peptide VVRP, or peptides comprising said sequence VVRP.

Kohmura

Kohmura et al. describe fragments of human κ casein, in particular peptide having sequence VVRP (i.e., a peptide of the instant invention). See p. 835, Table 1, compound No. 6. Further, the reference teaches peptides comprising said sequence VVRP: AVVRP, PAVVRP, NPAVVRP, ANPAVVRP, YANPAVVRP (i.e., peptides as instantly claimed, wherein ψ= 1÷5, Ω=0). See p. 835, Table 1, compounds No. 7-11. The referenced peptides exhibit a strong inhibitory effect on angiotensin-converting enzyme (ACE), the latter being an important regulator of blood pressure (see, e.g., p.835, second column). Kohmura does not teach administration of the referenced peptides in a form of pharmaceutical composition.

Goodman & Gilman's

Goodman & Gilman's "The pharmacological basis of therapeutics" (the reference is submitted by applicants) teaches that the most frequently used ways of administration of ACE inhibitors is oral or intravenous. See pages 745, 746. Also, the reference teaches that there is no compelling reason to favor one ACE inhibitor over another, since all ACE inhibitors have ... similar therapeutic indications, adverse effect profiles and contraindications." See p. 745, first full paragraph.

Cho et al (US 5,665,700)

'700 patent teaches that various polypeptides can be administered orally in the form of water-in-oil formulations. See claims 1-3,20.

It would be *prima facie* obvious to one skilled in the art to be motivated to prepare pharmaceutical compositions from peptides of Komura because they have a desirable pharmaceutical properties of ACE inhibitors. Selection of a particular physical form of delivery would be within a perview of a person skilled in art. For example, an artisan would be motivated to use water-in-oil formulation which has proven to be effective for oral administration of various types of polypeptides, as illustrated in US 5,665,700.

In regard to intended use recited in the preamble of claim 1, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. A mere statement of purpose or intended use in the preamble of a claim need not be considered in finding anticipation Divertech Corp. V. Century Steps, Inc.,7USPQ2d 1315 (Fed. Cir. 1988); In re Stencel, 4 USPQ2d 1071 (Fed. Cir. 1987). The motivation in the prior art to combine references need not be identical to that of the applicant to establish obviousness. In re Kemps, 40 USPQ2d 1309 (Fed. Cir., 1996). Further, the discovery of a new use for a prior art composition based on previously unknown properties of the structure may be patentable if claimed as a method; in the instant case the claims are drawn to a composition.

5. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, item (2), are drawn to compositions comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that peptides resulting from substitution of a Val residue in VVRP peptide taught in Kohmura with Ile, Leu, or Met residues will have similar biological activity and thus be also useful in pharmaceutical preparations.

6. Claims 1, 3, 4 remain rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al, supra., and further in view of Bundgaard (Design of Prodrugs, Chapter 1, 1985) and Sumner-Smith (US 5,646,120). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, items (5-7), are drawn to compositions comprising peptide comprising sequence VVRP peptide and having acetyl protective group at N-terminus and/or amido group at C-terminus.

The Kohmura reference is applied as above. It is well known in the peptide art to administer peptide in a form of their prodrugs which have protected N- and/or C- termini because such

substitution allows to optimize their solubility and/or stability and make them more suitable for pharmaceutical applications. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymatic catalysis. See Bundgaard, p. 1. Sumner-Smith is cited to illustrate use of acetyl group to protect NH_2 terminal group, and amido-group, to protect COOH terminal group in peptides prepared for *in vivo* administration. See col. 2, lines 45-52,col. 6, lines 42-50, 53-62. Therefore, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use peptides described by Kohmura in pharmaceutical compositions in a form of a prodrug analog having protected N- and/or C-termini with a reasonable expectation that such prodrugs will have at least similar effectiveness in inhibition of angiotensin-converting enzyme and regulation of related physiological processes.

7. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Steffens et al. (US Patent 5,681,721) in view of "Remington Pharmaceutical Sciences" and WPIDS abstract 1978-34432 (JP 53034915) .

The instant claims, in part defined in claim 1, item (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP.

Proteins comprising sequence VVRP are well described in the prior art: Search in Registry file of STN Database produced 396 hits. Steffens et al reference is used as a representative.

Steffens

Steffens teaches bifunctional urokinase variants having improved fibrinolytic characteristics and thrombolytic pharmaceutical compositions comprising thereof. See claims 1, 18. In particular, the reference teaches protein

1 SKTCYEGNGH FYRGKASTDT MGRPCLPWNS ATVLQQTYHA HRSDALQLGL
51 GKHNYCRNPD NRRRPWCYVQ VGLKPLVQEC MVHDCADGKK PSSPPEELKF
101 QCGQKTLRPR FKIIGGEFTT IENQPWFAAI YRRHRGGSVT YVCGGSLISP
151 CWVISATHCF IDYPKKEDYI VYLGRSRLNS NTQGEMKFEV ENLILHKDYS
201 ADTLAHHNDI ALLKIRSKEG RCAQPSRTIQ TICLPSMYND PQFGTSCEIT
251 GFGKENSTDY LYPEQLKMTV VKLISHRECQ QPHYYGSEVT TKMLCAADPQ
301 WKTDSCQGDS GGPLVCSLQG RMTLTGIVSW GRGCALKDKP GVYTRVSHFL
351 PWIRSHTKEE NGLALSPVVV VVRPLGGGGN GDFEEIPEEY LQ

having VVRP moiety at positions 371-374 (underlined). See col. 11, compound M28.

The pharmaceutical composition of Steffens reads on the instantly claimed composition comprising peptides comprising VVRP sequence, except for the limitation "water-in-oil", added in the amended claim. Anyone would be capable of preparing a composition from a known compound and to select a proper formulation. See, e.g., "Remington Pharmaceutical Sciences", part 8, Mack Publishing Co., Easton, PA, 1980. Further, in regard to water-in-oil form of composition, such form is customary for pharmaceutical compositions. WPIDS abstract 1978-34432 (JP 53034915) is cited to illustrate use of water-in-oil formulation for intravenous injection of thrombolytic agents.

In regard to intended use recited in the preamble of claim 1, arguments related to the intended use of the composition are of little relevance in determining the patentability of the composition. A mere statement of purpose or intended use in the preamble of a claim need not be considered in finding anticipation Divertech Corp. V. Century Steps, Inc.,7USPQ2d 1315 (Fed. Cir. 1988); In re Stencel, 4 USPQ2d 1071 (Fed. Cir. 1987). The motivation in the prior art to combine references

need not be identical to that of the applicant to establish obviousness. In re Kemps, 40 USPQ2d 1309 (Fed. Cir., 1996). Further, the discovery of a new use for a prior art composition based on previously unknown properties of the structure may be patentable if claimed as a method; in the instant case the claims are drawn to a composition.

8. Claims 1, 3 are rejected under 35 U.S.C. 103(a) as obvious over Steffens et al., supra., and further in view of Atlas of Protein Sequence and Structure (Vol. 5, 1972). The rejection is maintained for the following reasons of record.

The instant claims, in part defined in claim 1, items (2), (4), are drawn to compositions comprising protein with molecular weight of between approximately 0.5 and 100 kD, said protein comprising oligopeptide VVRP wherein one of Val residues is replaced by leucine or isoleucine, or methionine residues. It is well known that several amino acids are considered to conservative substitutions of Val. These amino acids include Leu, Ile and Met. Atlas of Protein Sequence and Structure, p. 96, is cited to show that such amino acids are known conservative substitutions of Val (see col. 8). Therefore, in view of the equivalence of Val, Ile, Leu, and Met, the use of Ile, Leu or Met amino acid residues in place of Val in the primary reference would have been obvious to one of ordinary skill in the art at the time the invention was made. One would expect, in the absence of evidence to the contrary, that proteins resulting from substitution of a Val residue in VVRP moiety in the protein taught by Steffens with Ile, Leu, or Met residues will have similar biological activity.

9. Claims 1, 6,11,12 are rejected under 35 U.S.C. 103(a) as obvious over Kohmura et al., supra, or Steffens et al., supra. The rejection is maintained for the following reasons of record

The instant claims are drawn to concentration range, 0.000001-10%, of compositions defined in claim 1.

The references are applied as above, see preceding paragraphs 6-10.

In regard to particular concentration ranges of the active ingredient in composition, Kohmura teaches that IC_{50} concentration of the referenced peptides is in the range 8-80μM, which corresponds to about 0.0005 - 0.005% (as compared to 0.000001 - 10% claimed range). Steffens et al use pharmaceutically effective concentrations (claim 18), which are presented in the reference in concentration units different from those instantly claimed. If there are any differences between Applicant's claimed preparations and that of the prior art, the differences would appear to be minor in nature. The instant invention's preparations, which fall within the scope of the prior art compositions, would have been *prima facie* obvious from said prior art disclosure to a person of ordinary skill in the art at the time the invention was made because, in the absence of sufficient factual evidence or unexpected results to the contrary, Applicant's claims are directed to optimization of an "art recognized variable" which is well within the perview of one of ordinary skill in the art.

Conclusion.

10. No claims are allowed

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (703) 305-4506. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (703) 308-4028. The fax telephone number for this group is (703) 305-3014. Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

May 21, 1999

MICHAEL BORIN, PH.D
PRIMARY EXAMINER